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Design, Synthesis and Biological Activities of New Strobilurin Derivatives Containing Substituted Pyrazoles

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Design, Synthesis and Biological Activities of New Strobilurin Derivatives Containing Substituted Pyrazoles

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ABSTRACT:

BACKGROUND: Strobilurins are one of the most important classes of agricultural fungicides. To discover new strobilurin analogues with high activity, a series of new strobilurin derivatives containing substituted pyrazoles in the side chain were synthesized and bioassayed.

RESULTS: The compounds were identified by ¹H nuclear magnetic resonance (NMR), IR, MS and elemental analysis. Preliminary bioassays indicated that some title compounds exhibited excellent fungicidal activities against *Pseudoperonospora cubensis* protecting cucumber and *Erysiphe graminis* protecting wheat at 6.25 and 1.56 mg L⁻¹, respectively, and showed a moderately high acaricidal activity against *Tetranychus cinnabarinus* at 20 mg L⁻¹. The relationship between structure and biological activity is discussed in terms of effects of the substituent of the pyrazole ring.

CONCLUSION: The present work demonstrates that strobilurin analogues with substituted phenylpyrazolylmethoxymethyl side chains can be used as possible lead compounds for further developing novel fungicides and acaricides.

KEYWORDS: strobilurin derivatives; fungicidal activity; acaricidal activity

1. INTRODUCTION

Strobilurins have become one of the most important classes of agricultural fungicides since azoxystrobin (**1**) was launched first in 1996.^{1,2} The fungicidal activity is exhibited by blocking the respiratory chain electron transfer between cytochrome b and cytochrome c₁. More than ten strobilurin fungicides have been manufactured commercially to date including azoxystrobin (**1**) and pyraclostrobin (**2**).^{1,2} In spite of the fact that the mechanism of respiratory chain electron transfer does not differ significantly among fungi, mites, and insects, practically no strobilurin derivative with significant acaricidal and insecticidal activity has been identified³ except for fluacrypyrim (**3**), an acaricide for fruit protection.⁴

We have been studying to develop new strobilurin analogues. Our aim has been primarily to obtain compounds that are active more than analogues ever known, hopefully against resistant fungal strains. Acaricidal and insecticidal analogues have also been looked for as possible targets. We have designed a virtual structure (**4**) by combining structural components taken from highly potent pyraclostrobin (**2**) and acaricidal fluacrypyrim (**3**) as shown in **Figure 1**. The candidate structure (**4**) inherits the "methyl (*E*)- β -methoxyacrylate" moiety from azoxystrobin (**1**) and fluacrypyrim (**3**), and shares the *N*-heteroaryloxymethyl substituent at the position ortho to the "methyl methoxyester" pharmacophore with fluacrypyrim (**3**) and pyraclostrobin (**2**). In fact, the structure of the *N*-heteroaromatic ring within our ortho aryloxymethyl substituent is closely similar to, but certainly different from, that existing in pyraclostrobin (**2**). We have synthesised a number of candidates (**4**) with variously substituted phenyl moiety and the pyrazole ring with methyl and dimethyl modifications.

We have found that some synthesised compounds display an excellent fungicidal activity against *P. cubensis* and *E. graminis* protecting respective crops being comparable to such standard fungicides as azoxystrobin and kresoxim-methyl (**Figure 2**)⁵. Additionally, some others exhibit an acaricidal activity against *T. cinnabarinus* comparable with and higher than a reference acaricide, pyridaben (**Figure 2**)⁶.

2. EXPERIMENTAL

2.1. General

All starting materials and reagents were commercially available and used without further

purification except as indicated. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H NMR spectra were recorded with Mercury 300 (Varian, 300 MHz) spectrometer with CDCl_3 as the solvent and TMS as the internal standard. Infrared spectra were measured with KBr discs using a PF-983G instrument (Perkin-Elmer). Mass spectra were recorded using a JEOL JMS-700 mass spectrometer.

All compounds were tested for control of the rice blast (*Pyricularia oryzae*) on "Jingang 30" rice, cucumber gray mold (*Botrytis cinerea*) and cucumber downy mildew (*Pseudoperonospora cubensis*) on "Changchun Mici" cucumber, wheat powdery mildew (*Erysiphe graminis*) on "Liaochun 10" wheat and spider mites (*Tetranychus cinnabarinus*) on kidney bean. All fungal, plant, and mite materials were obtained from pesticide discovery group in Shenyang Research Institute of Chemical Industry.

2.2. Synthesis of title compounds

According to known methods,⁷ substituted β -keto esters (**6**) were prepared from substituted ketones (**5**) [substituted acetophenones (**5**: $\text{R}_4 = \text{H}$) and propiophenones (**5**: $\text{R}_4 = \text{Me}$)] and dimethyl carbonate. The ester (**6**) and methyl hydrazine were dissolved in methanol and the mixture was heated to reflux to obtain the substituted 5-hydroxy-1*H*-pyrazole (**7**).⁸ The strobilurin analogues (**8–35**) were prepared by reacting the intermediate pyrazoles (**7**) with methyl (*E*)-2-[2-(bromomethyl)phenyl]-3-methoxyacrylate under basic conditions as shown in **Figure 3**.

2.2.1. General procedure for the synthesis of intermediate β -keto esters (**6**)

A suspension of 60% sodium hydride (4.0 g, 0.1 mol, washed with petroleum ether) in a mixture of dimethyl carbonate (4.95 g, 0.055 mol) and 100 mL tetrahydrofuran was heated to reflux for 0.5 hr. A solution of the substituted phenylketones (**5**) (0.05 mol) in 100 mL tetrahydrofuran was added dropwise for 0.5 hr at refluxing. When the reaction mixture became clear, it was refluxed further for 4–5 hr. Then, the mixture was cooled and acidified with 36.5% hydrochloric acid, and filtrated. The filtrate was poured into a large amount of water, extracted 3 times with ethyl acetate. The combined extracts were washed with brine, dried, and concentrated under vacuum to obtain the crude oily product.

2.2.2. General procedure for the synthesis of intermediate pyrazoles (**7**)

Each of β -keto esters (**6**) was dissolved in methanol and heated to reflux. Methyl hydrazine was

added dropwise to the reaction solution. The process of the reaction was monitored by thin-layer chromatography (TLC). The reaction solution was evaporated, cooled, and the filtered solid was washed with methanol, dried, and crystals were obtained.

2.2.3. Procedure for the synthesis of (*E*)-methyl 2-(2-((3-(4-chlorophenyl)-1-methyl-1*H*-pyrazol-5-yloxy)methyl)phenyl)-3-methoxyacrylate (**9**)

3-(4-Chlorophenyl)-1-methyl-1*H*-pyrazol-5-ol (1.03 g, 4.96 mmol) was dissolved in 5 mL of DMF, and 60% sodium hydride (0.36 g, 9.00 mmol, washed with petroleum ether) was added to the solution. The solution was stirred for 0.5 hr, and methyl (*E*)-2-[2-(bromomethyl)phenyl]-3-methoxyacrylate (1.38 g, 4.98 mmol) was added. The reaction mixture was heated to 80°C and was monitored by TLC. At completion of the reaction (after 3 hr), the mixture was added to 50 mL of brine, and extracted 3 times with 100 mL of ethyl acetate. The combined organic extracts were dried, and concentrated to obtain the crude product. It was purified via silica gel column chromatography, using a 1:4 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range: 60-90 °C) as the eluting solution to obtain Compound **9** as viscous oil which solidified to give 1.51 g colorless crystals.

IR(KBr)v: 2940 (s, C-H), 1695 (s, C=O), 1630 (s, C=C), 1550, 1510 (w, aromatic rings), 1430 (s, CH₃), 1250, 1200 (m, C-N), 1140 (s, C-O), 840, 770, 750 (s, Ph-H) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (m, 2H, 3-Ph-2,6-2H), 7.62 (s, 1H, CH), 7.52 (m, 1H, Ph-6-H), 7.38 (m, 4H, 3-Ph-3,5-2H+Ph-3,5-2H), 7.21 (m, 1H, Ph-4-H), 5.76 (s, 1H, Py-4-H), 5.05 (s, 2H, CH₂), 3.84 (s, 3H, NCH₃), 3.75 (s, 3H, CO₂CH₃), 3.72 (s, 3H, OCH₃); Anal. Calcd for: C, 64.00; H, 5.13; N, 6.79; Found: C, 64.09; H, 5.11; N, 6.76.

2.2.4. Procedure for the synthesis of (*E*)-Methyl 2-(2-((3-(2,4-dimethylphenyl)-1,4-dimethyl-1*H*-pyrazol-5-yloxy)methyl)phenyl)-3-methoxyacrylate (**29**)

3-(2,4-Dimethylphenyl)-1,4-dimethyl-1*H*-pyrazol-5-ol (1.08 g, 5.00 mmol) was dissolved in 5 mL of DMF, and anhydrous potassium carbonate (1.38 g, 10.00 mmol) was added to the solution. The solution was stirred for 0.5 hr, and methyl (*E*)-2-[2-(bromomethyl)phenyl]-3-methoxyacrylate (1.39 g, 5.00 mmol) was added. The reaction mixture was heated to 80°C and was monitored by TLC. Three hours later, the mixture was cooled and diluted with 50 mL of brine, and extracted 3 times with 100 mL of ethyl acetate. The combined organic extracts were dried, and concentrated to obtain the crude product. It was purified *via* silica gel column chromatography, using a 1:4 (v/v) mixture of ethyl acetate and petroleum ether (boiling point range: 60-90 °C) as the eluting solution to yield Compound **29** (1.35 g) as viscous oil.

IR(KBr)v: 2930 (s, C-H), 1710 (s, C=O), 1630 (s, C=C), 1500 (w, aromatic rings), 1450 (s, CH₃), 1250, 1190 (m, C-N), 1130 (s, C-O), 820, 770, 740 (s, Ph-H)cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (m, 1H, 3-Ph-6-H), 7.59 (s, 1H, CH), 7.35 (m, 2H, 3-Ph-3-H+Ph-6-H), 7.17 (m, 2H, Ph-3,5-2H), 7.05 (m, 2H, 3-Ph-5-H+Ph-4-H), 5.16 (s, 2H, CH₂), 3.81 (s, 3H, NCH₃), 3.68 (s, 3H, CO₂CH₃), 3.44 (s, 3H, OCH₃), 2.37 (s, 3H, Ph-2-CH₃), 2.10 (s, 3H, Ph-4-CH₃), 1.73 (s, 3H, Py-4-CH₃); Anal. Calcd for: C, 71.41; H, 6.71; N, 6.66; Found: C, 71.37; H, 6.78; N, 6.63.

2.3. Fungicidal assay^{9,10,11}

The compounds were dissolved in a 9:1 mixture of acetone and water, and achieve various appropriate concentrations. The solution was sprayed onto plants and allowed to dry for two hours. Then, the plants were inoculated with fungal spores. Each test utilized control plants which were sprayed and "inoculated" with the appropriate solvents only. For fungicidal tests, the plants were inoculated one day after treating the plants with the compounds. The results are represented as the percent disease control as compared to the untreated check where one hundred was rated as the complete disease control and zero as no disease control.

2.3.1. Against Rice Blast (RB)

Cultures of *Pyricularia oryzae* were maintained on potato dextrose agar (PDA) for two to three weeks. The spores were washed from the agar with water containing 1 drop of Tween 80 per 100 mL. After filtering the spore suspension through two layers of cheesecloth, the spore count was adjusted to 5×10⁵ spores mL⁻¹. The spore suspension was sprayed onto 12-day old rice plants, cultivar "Jingang 30", using a DeVilbiss atomizer, which had been used for spraying fungicidal solutions. The inoculated plants were placed in a dew chamber (R.H. >95%) at 20 °C for 36 hr to allow for infection. After the infection period, the plants were placed in the greenhouse. After 6 days, the effect of fungicides was scored as the disease control value.

2.3.2. Against Cucumber Gray Mold (CGM)

Cucumber plants, cultivar Changchun Mici, were maintained in the greenhouse. Large, fully expanded leaves were collected from the plants. They were placed in a large petri plate (15-cm. diameter) being supported by glass rods, and the stems were wrapped with cotton. The upper cover of the plate was removed and the upper surface of the detached cucumber leaf was sprayed with the fungicide solutions. The leaves were allowed to dry in the air for approximately 2 hr. The cultures of *Botrytis cinerea* were maintained on potato dextrose agar for two to three

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5 weeks. Agar plugs, 6 mm in diameter, were cut with a cork borer from the periphery of the fungal
6 colony margin, and placed with the fungal surface in contact with the treated upper surface of the
7 cucumber leaf. Each leaf received two mycelial plugs. After placing the petri plate cover over the
8 leaves, the plates were constantly maintained in an environmentally controlled chamber at 20°C,
9 and 90% humidity for four days. The average lesion size on treated leaves was measured and
10 compared to that produced on the control leaves. Data were expressed as percent control.
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15 16 **2.3.3. Against Cucumber Downy Mildew (CDM)**

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19 Cucumber plants, cultivar Changchun Mici, with one fully expanded true-leaf were maintained in a
20 greenhouse. After spraying with the fungicide solution, the plants were allowed to dry in the air
21 for approximately 2 hr. The cultures of *Pseudoperonospora cubensis* were maintained on
22 cucumber plants. After collecting the spores by shaking the leaves in water, the lower surface of
23 the treated cucumber leaves were sprayed with a spore suspension of ca. 100,000 spores per mL.
24 The plants were transferred to a thermo-hygrostat kept at 20°C and >90% humidity for five days
25 for infection. After five days placed in the greenhouse further, the plants were examined for the
26 disease control score.
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34 **2.3.4. Against Wheat Powdery Mildew (WPM)**

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37 *Erysiphe graminis* (f. sp. *Tritici*) was cultured on wheat seedlings, cultivar "Liaochun No.10", in a
38 temperature-controlled room at 18°C. Mildew spores collected from the infected culture plants
39 were sprayed onto 7-day old wheat seedlings, which had been sprayed with the fungicide solution.
40 The inoculated seedlings were kept in a controlled temperature room at 18°C with subirrigation.
41 The percent disease control was rated 7 days after the inoculation.
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47 **2.4. Acaricidal test**

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50 Each of test compounds was first dissolved in a certain amount of mixture of acetone and water,
51 and then water containing 0.1 % Tween 80 were added to make the stock solution. Serial test
52 solutions were prepared by using a mixture of acetone and water (9:1). Kidney bean plants with
53 one true-leaf were infested with carmine spider mites (*Tetranychus cinnabarinus*) prior to spraying.
54 An airbrush was used for spraying compound solution, and three replicates were set for each
55 treatment. After plants were dried, they were transferred to a maintaining room for observation.
56 The mortality of spider mites was scored as percent control by visual inspection 48 hr after the
57 spray treatment.
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3. RESULTS AND DISCUSSION

3.1. Chemistry

According to procedures exemplified in Sections 2.2.3 and 2.2.4, strobilurin derivatives were synthesized mostly with a good overall yield of 60–75%, as shown in **Table 1** (for 3-substituted-phenyl-1-methyl-1*H*-pyrazol-5-yloxy analogues, **8–24**) and **Table 2** (for 3-substituted-phenyl-1,4-dimethyl-1*H*-pyrazol-5-yloxy analogs, **25–35**). The synthesised compounds were characterized by ¹H NMR, IR and elemental analyses. All spectral and analytical data were consistent with the assigned structures. The IR spectra of compounds showed C-H and C=O stretching bands at 2920–2960 and 1700–1720 cm⁻¹, respectively. The synthesis of the p-Cl-biphenyl compound **23** was achieved via a Pd/C-catalysed Suzuki coupling reaction of 4-chlorophenylboronic acid and the 4-bromophenyl compound **10**.

3.2. Biological activity

3.2.1. Fungicidal activity

As indicated in Table 1, many of synthesised compounds exhibit fairly potent activity against *P. oryzae*, *B. cinerea*, *P. cubensis*, and *E. graminis*. Methylpyrazolyloxy analogues in **Table 1** (abbreviated as the Me series, hereafter) seem to be slightly less potent than corresponding dimethylpyrazolyloxy analogues in **Table 2** (abbreviated as the Me₂ series) sharing common substituted phenyl groups, although there are a few exceptional patterns such as the pair of 4-Cl-Ph analogues (**9** and **26**). Under equivalent dosage conditions of 400 mg L⁻¹, most of the two series of analogues show 100 % inhibition against *P. cubensis* and *E. graminis*, whereas they do not against *P. oryzae* and *B. cinerea*, many being inactive. Therefore, the activity against *P. cubensis* and *E. graminis* was measured in the lower concentration range sequentially.

Because of the paucity of the dose-potency data, detailed structure-activity discussion for the activity against *P. oryzae* and *B. cinerea* is almost impossible. It appears, however, that there are an optimal hydrophobicity and/or a sterically acceptable limit of substituents at values for the dimethyl substitution in Compounds **14,15,28,29**, and **30**, and that the steric effect of alkoxy groups might be exerted by the shortest width (by that of oxygen) as observed in a higher activity of Compounds **18,19,33,34**, and **35**. Similar structure-activity speculations could apply to the activity against *P. cubensis* and *E. graminis*. Highly potent compounds at the lowest dosages

mostly overlap with those of which the activity against *P. oryzae* and *B. cinerea* is highest mentioned just above. In addition, an electron-withdrawing effect of substituent could be involved as suggested by a higher activity of 4-Cl-Ph (**9**), 4-Br-Ph (**10**), 4-F-Ph (**11**), and 4-NO₂-Ph (**22**) analogues of the Me series, and 4-Cl-Ph (**26**) analogue from the Me₂ series. As indicated above, the behaviour of the 4-Cl-Ph group is peculiar in that it is particularly favourable in enhancing the potency against *P. cubensis* when introduced into the skeleton of Me series (in compound **9**), but that it is reversed for the potency against *E. graminis* when exists in the Me₂ series (in compound **26**). Overviewing the structure-potency data, Compounds **9**, **14**, and **15** of the Me series and Compounds **28**, **29**, and **33** of the Me₂ series are regarded to be more potent and broader in the activity spectra than others.

Because the activities were measured *in vivo*, effects of metabolism and/or biotransformation inside the bodies of plant/fungus and acarids are inevitable in apparent potency variations. The inference that the electron-withdrawing substituents of the phenyl moiety seem to enhance the potency could be related to the fact that they tend to retard mechanisms of oxidative metabolism occurring on (or close to) the benzene ring^{12,13}. The higher the electronic (negative) charge within the ring system, the easier would occur such an oxidative detoxication metabolism as hydroxylation of the benzene ring. The fungicidal activity of two commercial fungicides, azoxystrobin and kresoxim-methyl, is also shown in Table **2**, indicating that the activity of our compounds is slightly higher than or comparable to that of these reference compounds.

3.2.2. Acaricidal activity

The acaricidal data are also shown in Tables **1** and **2**. The potency of majority of the Me series compounds is not noteworthy in Table **1**, whereas most compounds of the Me₂ series are 100 % effective at the dose of 600 mg L⁻¹ in Table **2**. From the dose-potency patterns in Tables **1** and **2**, it looks like the effect of substituted-phenyl substituents on the acaricidal potency is somewhat similar to that in the fungicidal activity against *P. cubensis*. Physicochemical effects of substituents as speculated in fungicidal activity could also be at work in governing the variations in the acaricidal potency. Compounds **10** (the 4-Br-Ph analogue of the Me series) and **29** (the 2,4-Me₂-Ph analogue of the Me₂ series) are among the most active as acaricides. In Table **3**, the potency of Compound **29** is compared with that of pyridaben⁶ (an inhibitor of mitochondrial electron transport) as the reference. Below the dose level of 20 mg L⁻¹, the potency of Compound **29** is significantly higher than that of the reference.

3.2.3. Field trials against *P. cubensis* of Compound **9**

The 4-Cl-Ph compound **9** of the Me series is one of the most potent and broadest spectral compounds in fungicidal activity as mentioned in Section **3.2.1**. It is particularly potent against *P. cubensis* exhibiting 100 % inhibition down to the dose of 3.12 mg L⁻¹ as shown in Table **1**. Expecting the agricultural utilization, we have carried out registration field trials of this compound against *P. cubensis* (cucumber downy mildew) in 2006 and 2007 as summarized in Table **4**. In Shanxi and Liaoning Provinces, the fungicidal activity of Compound **9** as 20% suspension concentrate (SC) is almost equivalent to that of azoxystrobin as 25% (SC), and, in Beijing area and Inner Mongolia, Compound **9** is significantly more potent than the reference azoxystrobin under equi-dosage conditions of the active ingredient in formulations. The activity of Compound **9** is also much higher than that of metalaxyl (Figure **2**)¹⁴ as 25% wettable powder (WP).

4. CONCLUSIONS

As described above, quite a few strobilurin analogues synthesized by introducing various substituted-phenyl groups into the pyrazole ring of the designed skeletal lead were indeed active fungicidally against *P. oryzae*, *B. cinerea*, *P. cubensis* and *E. graminis*. Some of them were not only more potent than such reference strobilurin compounds as azoxystrobin and kresoxim-methyl but also acaricide-active more potently against *T. cinnabarinus* than the reference pyridaben. As discussed in sections **3.2.1** and **3.2.2**, variations in the apparent potency are associated with hydrophobic, steric, and electronic effects of substituents in the phenyl moiety not only on the target activity but also on the metabolic detoxication mechanisms. These factors are accumulated resulting in somewhat perplexing total substituent effects and structure-activity patterns. Understanding this situation, further analogue syntheses and structure optimisation studies are in progress.

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Supporting Information Available: ¹H NMR, IR, and element analysis data for the target compounds. This information is available free of charge via the Internet in Wiley InterScience at <http://www.interscience.wiley.com/jpages/1526-498X/suppmat/>

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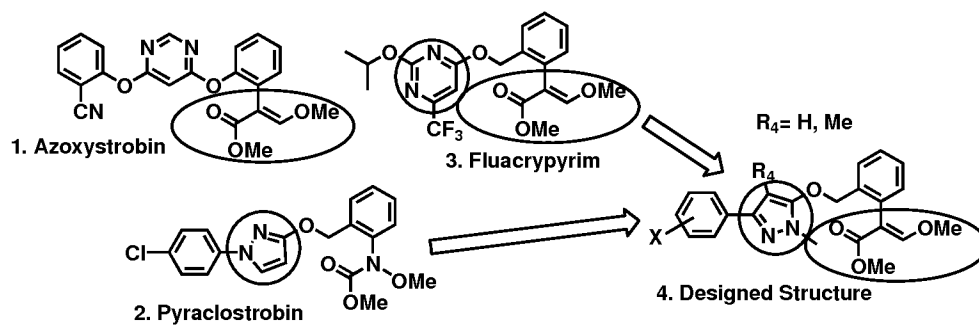


Figure 1. Design of Skeleton

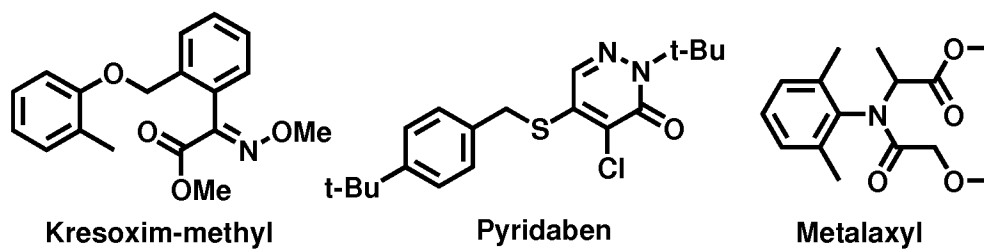


Figure 2. Reference Compounds

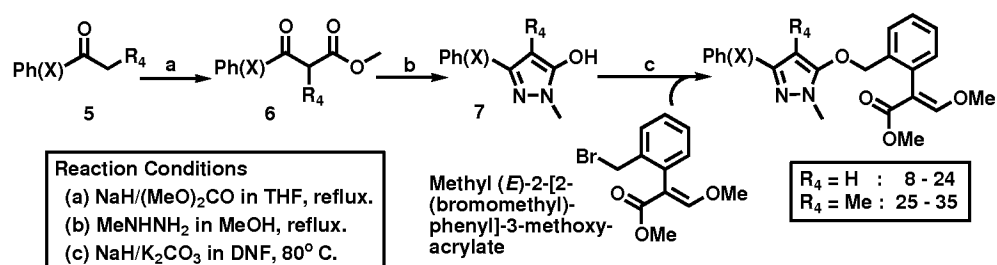


Figure 3. Synthesis

Table 1 Biological Activity of 3-substituted-phenyl-1-methyl-1*H*-pyrazol-5-yl-oxy analogues **8–24**

Strobilurin Analogues				Biological Activity (% control at given concentration mg/L)												
Cpd #	Substituents		mp (°C)	Yield (%)	Fungicidal Activity						Acaricidal Activity					
	R ₄	X			P. oryzae		B. cinerea		P. cubensis		E. graminis		T. cinnabarinus			
					400	400	400	25	6.25	3.12	400	12.5	1.56	600	150	38
8	H	H	123-127	69	0	0	100	0	0	0	100	0	0	0	/	/
9	H	4-Cl	124-126	73	100	100	100	100	100	100	100	75	0	100	0	0
10	H	4-Br	104-106	66	70	0	100	100	85	60	100	100	10	100	71	57
11	H	4-F	107-109	63	50	100	100	100	100	75	30	/	/	0	/	/
12	H	4-Me	oil	70	0	0	100	0	0	0	100	35	0	0	/	/
13	H	4-t-Bu	oil	71	100	50	100	15	/	/	70	/	/	0	/	/
14	H	3,4-Me ₂	100-102	64	100	50	100	100	40	35	100	100	80	100	0	0
15	H	2,4-Me ₂	oil	65	100	50	100	100	70	20	100	100	80	100	0	0
16	H	2,4-Cl ₂	154-157	69	0	0	100	100	45	20	100	100	0	0	/	/
17	H	4-MeS	126-129	66	90	0	100	100	35	0	0	/	/	0	/	/
18	H	4-MeO	127-131	65	100	50	95	90	15	0	100	65	0	0	/	/
19	H	2-MeO	oil	65	100	50	100	50	0	0	100	100	35	0	/	/
20	H	2-Cl	oil	66	0	0	100	100	0	0	100	100	40	100	0	0
21	H	4-CF ₃ CH ₂ O	92-94	77	0	0	100	90	0	0	60	/	/	0	/	/
22	H	4-NO ₂	162-164	67	99	0	100	100	70	50	100	100	95	0	/	/
23	H	4-(4-Cl-Ph)	oil	61	0	0	100	100	0	0	100	95	0	0	/	/
24	H	4-PhO	161-163	70	0	0	100	100	0	0	0	/	/	0	/	/

"/" : Not measured.

Table 2 Biological Activity of 3-substituted-phenyl-1,4-dimethyl-1*H*-pyrazol-5-yloxy analogues **25-35**

Strobilurin Analogues				Biological Activity (% control at given concentration mg/L)														
Cpd #	Substituents		mp (°C)	Yield (%)	Fungicidal Activity												Acaricidal Activity	
	R ₄	X			P. oryzae	B. cinerea	P. cubensis				E. graminis				T. cinnabarinus			
					400	400	400	25	6.25	3.12	400	12.5	1.56	600	150	38		
25	Me	H	oil	61	0	0	100	100	60	40	100	100	55	100	0	0		
26	Me	4-Cl	69-72	62	0	0	95	0	0	0	100	100	100	60	/	/		
27	Me	4-Me	oil	72	0	0	100	100	75	40	100	100	45	100	0	0		
28	Me	3,4-Me ₂	oil	66	100	50	100	100	85	30	100	100	70	100	80	0		
29	Me	2,4-Me ₂	oil	64	100	50	100	100	98	80	100	100	90	100	100	100		
30	Me	2,5-Me ₂	oil	67	100	50	100	80	0	0	100	50	0	100	20	0		
31	Me	4-Et	oil	65	0	0	100	100	60	20	100	100	0	100	100	30		
32	Me	4- <i>t</i> -Bu	oil	62	50	50	95	20	0	0	90	10	0	100	0	0		
33	Me	4-MeO	oil	63	100	100	100	100	96	55	100	100	95	90	0	0		
34	Me	4-EtO	100-102	68	100	100	100	50	0	0	100	100	65	100	35	20		
35	Me	4-CF ₃ CH ₂ O	137-139	67	100	100	100	40	0	0	100	100	65	60	/	/		
AZS ^a					100	100	100	100	95	100	100	100	60	NA	NA	NA		
KSM ^b					100	100	/	35	0	0	100	100	100	NA	NA	NA		

"/": Not measured. a: azoxystrobin, b: kresoxim-methyl, NA: Not applicable.

Table 3. Acaricidal activity against *T. cinnabarinus* (% mortality, 48 hr)

Conc. (mg L ⁻¹)	40	20	10	5	2.5	1.25
Compound 29	100	100	89	85	36	28
Pyidabn	77	57	48	22	12	0

Table 4. The field trial results of compound **9** against *P. cubensis* in 2006 and 2007 (% control)

Cpds	Dose g.a.i./ha	Shanxi		Beijing		Inner Mongolia		Liaoning	
		2006	2007	2006	2007	2006	2007	2006	2007
Cpd 9 20% SC	100	88	90	84	83	91	96	75	69
	50	85	85	78	80	81	93	65	73
	25	79	82	65	69	49	86	61	77
AZS 25% SC	100	92	82	73	75	77	93	74	74
Metalaxyl 25% WP	500	84	73	71	67	62	51	60	68